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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/465,802	12/17/1999	Mariano A. Garcia-Blanco	1579-321	9348

7590 12/20/2002

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	15

DATE MAILED: 12/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/465,802	Applicant(s) Garcia-Blanco
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 7, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *5* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *5* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13,14*
4) ☒ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Seq Listing Error Report*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

2. The Amendment filed August 12, 2002 (Paper No. 10), the Declaration filed August 12, 2002 in response to the Office Action of November 6, 2001 (Paper No. 8) are acknowledged and have been entered. Previously pending claims 1-4 have been canceled and new claim 5 has been added. Claim 5 is currently being examined.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Objection

Drawings

4. Figure 6A is objected to because, although the specification has been amended to recite SEQ ID Nos 34-44, it is not possible to determine which sequence is associated with which unique identifier. Applicant must label the Sequences disclosed in Figure 6A to uniquely identify each of the disclosed sequences.

5. Figure 8A is objected to because, although the specification has been amended to recite SEQ ID Nos 45-46, it is not possible to determine which sequence is associated with which unique identifier. Applicant must label the

Sequences disclosed in Figure 8A to uniquely identify each of the disclosed sequences.

6. Figure 8B is objected to because, although the specification has been amended to recite SEQ ID Nos 47 it is not possible to determine, given the teaching in the specification, whether SEQ ID NO:47 is rat or human. Further, only one of the sequences in Figure 8B has been given a SEQ ID NO. Appropriate correction is required. Further, Applicant must label the Sequences disclosed in Figure 8B to uniquely identify each of the disclosed sequences.

Specification

7. The specification on page 1 should be amended to reflect the status of the parent application. Appropriate correction is required.

8. A plethora of spelling errors have been noted in the specification, for example "alterative" on page 13, line 17. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where on the there informalities are to be found. Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

9. Claim 5 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is noted that the newly claimed limitation drawn to a method of determining the likelihood of metastasis of a prostate tumor is inherently drawn to a method of determining the metastatic potential of a prostate tumor in a patient. Therefore, it will be assumed for examination purposes that the claim as currently constituted is still drawn to a method of determining the metastatic potential of a prostate tumor in a patient.

The claims are drawn to a method of determining the likelihood of metastasis of a prostate tumor comprising assaying a tumor for FGF-R2 IIIc isoform mRNA, wherein expression of said isoform indicates that said tumor is likely to metastasize. The specification teaches that progression of human prostate cancer from androgen sensitive to an androgen insensitive tumor is accompanied by a change in alternative splicing of FGF-R2 (p. 13, lines 15-21). The invention also relates to a method of determining the metastatic potential of a prostate tumor in a patient (p. 13, lines 22-24). The specification teaches techniques for detection of the FGF-R2 IIIc transcript (pages 14-15) as well as antibody techniques for detection of proteins translated from the transcript (p. 15). The specification exemplifies the identification of Intronic Sequence Element wherein DT and AT3 cell lines were assayed for FGF-R2 isoforms and the androgen independent AT3 cell line was found to express only the IIIc isoform (see Example 1), as well as preparation of FGF-R2 specific antibodies (see Example 2).

One cannot extrapolate the teaching of the specification to the enablement of the claims because (1) the enablement of the claimed invention is based solely on *in vitro* Dunning Model cultured cell line data, (2) the specification provides

insufficient guidance on the ability of the claimed assay to determine the likelihood (that is predict) metastasis of a prostate tumor in a human.

(1) The *in vitro* experimental data presented is based on cells related to the DT and AT3, both of which are Dunning Model Cell lines. Applicant has clearly explained and demonstrated, with submitted references, the limitations of the Dunning model of prostate cancer in terms of mimicking the human condition. Applicant states that:

> Examiner is urged to "first consider the attached articles that underscore the limitations of the rat model used by Yan et al in terms of mimicking the human condition. For example, Tennant et al (2000)(page 296 underlined) points out that the metastatic pattern observed with these rat tumors are different than the one observed in human cancer. In addition, there has been a debate about the true origin of the Dunning tumors as discussed by Bostwick et al (2000) (page 291 underlined) and by Geobel et al (1992) (abstract attached). Weerden and Romjin (2000) clearly indicate that laboratory animals (dogs excepted) do not develop prostate tumors upon aging (page 263 underlined) (this is also reported by Bostwick)."

Given the limitations clearly disclosed by Applicant, it could not be predicted, nor would it be expected that the findings in these Dunning Model cell lines could be correlated to the human condition. Further, the *in vitro* experimental data presented is not commensurate in scope with the claimed invention since it is clearly not drawn to human tumor cells since the Dunning Model cells lines are derived from a rat prostate tumor (Yan et al, of record, p. 44513, col 2). Further, even if the cell lines were human cell lines, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts

in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. In addition, it is not clear whether the expression of the claimed mRNA in the exemplified AT3 cell line is an artifact of the cell culture system of this particular neoplastic cell line or whether this can be in any way related to the *in vivo* determination of the likelihood of metastasis of a prostate tumor in a human in view of the art recognized problems with artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in

culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:17797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Drexler et al further teach that only a few cell lines containing cells that resemble the in-vivo cancer cell have been established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, for the reasons set forth above, based on the cell culture data presented in the specification, it could not be predicted that, in the claimed invention

will function as claimed to determine the likelihood of metastasis of a prostate tumor.

2. Further, it is not clear why Applicant has concluded that expression of the FGF-R2 IIIc isoform is in any way sufficient or even necessary for determining the likelihood of metastasis of a prostate tumor. US Patent No. 5,830,640 specifically states that "the complexity of the processes involved in metastasis, and the lack of understanding of underlying molecular mechanisms, have made it particularly difficult .....to distinguish tumors that are likely to metastasize from those that are unlikely to do so" (col 2, lines 43-48). Van Weerden (The Prostate, 2000, 43:263-271) submitted by Applicant and therefore of record, specifically teaches that not much is known of the mechanisms involved in prostate tumor metastasis, mainly because of the lack of a suitable model system. This has resulted in an increased effort to develop metastatic model systems. So far, the results have been very limited (p. 268, col 2). Given the information in the specification and known in the art, the cell line system employed by Applicant does not appear to be a model system suitable to enable the claimed invention. Further, Applicant has not demonstrated any relationship between FGF-R2 IIIc isoform RNA expression and metastasis. Hill (The Basic Science of Oncology, Tannock et al Eds, McGraw Hill, NY, 1992, pp178-195) specifically teach that the relevance of various model systems to metastatic human tumors is often questioned, but the model systems are required for examination of specific aspects of the metastatic process. The interpretation of results must, however, recognize the limitations of the chosen model (p. 184, col 1). The process of metastasis includes the ability of the cells to

invade into and out of blood vessels, to survive in circulation, to arrest and to grow at a new site. Hill describes numerous types of assays for the determination of whether tumor cells are likely to metastasize (pages 184-185 see section 11.3.2) and further states that experimental metastasis assay tests the ability of cells to survive in circulation, to arrest in a target organ, to avoid host defenses, to invade a new organ, to establish new tumor growth. Although many properties are required for metastasis formation, one specific property may represent a "rate-limiting step" controlling the frequency of metastasis formation. It is possible that this rate-limiting property may be different for different tumors (para bridging pages 184-186). Given the art recognized controversy over whether the Dunning Model cell lines are even prostate tumor cells and the lack of guidance in the specification, it cannot be predicted that assay of claimed mRNA transcript would function as claimed. In view of the above, one of skill in he art would be forced into undue experimentation to practice the claimed invention.

Applicant's arguments, in part, drawn to the rejection of claims 1-4 under 35 USC 112, first paragraph in Paper No. 8, section 4, pages 3-6 are relevant to the instant rejection.

Applicant argues that (a) patent applicant enjoys the presumption that his/her invention can be practiced as claimed and that Examiner had not met the burden of providing evidence to the contrary, (b) the invention is based on the finding that in human prostate cancer, progression from an androgen sensitive tumor to an androgen insensitive tumor is accompanied by a change in alternative splicing of FGF-R2 so that FGF-R2 (IIIc) isoform is the predominant form of FGF-R2

expressed. Applicant further cites the Carstens et al, of record to demonstrate that there is no basis for Examiner's assertions regarding the lack of correlation between *in vitro* and *in vivo* results.

The arguments have been considered but are not persuasive (a') for the reasons previously set forth and because of the evidence presented above, (b') it is noted that the Carsten et al reference, similar to the instant application specifically states that expression of FGF-R2-III(c) is associated with loss of androgen sensitivity and progression of prostate disease. Carsten et al clearly demonstrate that lack of correlation between *in vitro* and *in vivo* results and that the cell culture data that they present is not predictable because the PC-3 cell line, which is androgen insensitive, does not produce FGF-R2-III(c) mRNA while the DU-145 cell line which is also androgen insensitive does. Further, Applicant is not claiming a method of assaying for alternative splicing but rather is claiming a method of determining the likelihood of metastasis of a prostate tumor and a review of the Carstens et al reference reveals that the reference is not commensurate in scope with the claimed invention because it is drawn to the determination of alternative splicing of FGF-R2 wherein the FGF-R2 (IIIc) isoform mRNA is found to be the predominant form of FGF-R2 in androgen insensitive cell lines and xenografts (see abstract). The results of the studies lead the authors to propose that loss of the IIIb isoform of FGF-R2 correlates with development of androgen insensitivity and progression of human prostate cancer (p.3060, col 2). It is clear that the paper is not drawn to the determination of likelihood of metastasis of prostate tumor in a human patient. Even if the paper were drawn to the likelihood of metastasis, the cell

line data would not be convincing for the reasons set forth above. Further, as drawn to the nude mouse xenograft models, Carstens et al specifically teach that the human prostate cancer cell xenografts were established by sc injection of primary cancer cells into nude mouse hosts (p. 3064, col 1) and that the xenografts were used because of the difficulties in using their approach in tumors *in situ* and because they felt that the xenograft tumors in nude mice represented a good model in which fairly uniform collections of prostate cancer cells could be collected and analyzed (p. 30610. The xenograft model data would not be convincing because van Weerden et al, of record teach that sc, iv, or ip injections of prostate tumor cells in nude mouse rarely result in metastases (p. 268, col 20). Thus, in the absence of objective evidence demonstrating the suitability of these xenograft models for direct correlation of metastatic studies to the human *in vivo* condition, it would not be expected that any of these xenograft would be suitable as models for determining the likelihood of metastasis. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

9. All other objections and rejections set forth in Paper No. 8 are withdrawn.

10. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
December 12, 2002